The Effects of Supplementation with α-Tocopherol and β-Carotene on the Incidence and Mortality of Carcinoma of the Pancreas in a Randomized, Controlled Trial

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BACKGROUND. Dietary components may be both causal and protective in cases of pancreatic carcinoma, but the preventive potential of single constituents has not been evaluated. The authors report the effects of α-tocopherol and β-carotene supplementations on the rates of incidence of and mortality from pancreatic carcinoma in a randomized, controlled trial.

METHODS. The 29,133 participants in the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study were male smokers who were ages 50–69 years at the time they were randomized into 1 of the following 4 intervention groups: dl-α-tocopherol (AT; 50 mg/day), β-carotene (BC; 20 mg/day), both AT and BC, and placebo. The daily supplementation lasted for 5–8 years. Incident cancers were identified through the national Finnish Cancer Registry and death certificates of the Statistics Finland. Results were analyzed by supplementation with Cox regression models.

RESULTS. Effects of both supplementations were statistically nonsignificant. The rate of incidence of pancreatic carcinoma was 25% lower for the men who received β-carotene supplements (n = 38) compared with the rate for those who did not receive β-carotene (n = 51) (95% CI, −51% to 14%). Supplementation with α-tocopherol (n = 51) increased the rate of incidence by 34% (95% CI, −12% to 105%) compared with the rate for those who did not receive α-tocopherol. Mortality from pancreatic carcinoma during the follow-up, adjusted for stage and anatomic location of the tumor, was 19% (95% CI, −47% to 26%) lower among those who received β-carotene and 11% (95% CI, −28% to 72%) higher among those who received α-tocopherol as compared with those who did not receive supplementation.

CONCLUSIONS. Supplementation with β-carotene or α-tocopherol does not have a statistically significant effect on the rate of incidence of pancreatic carcinoma or the rate of mortality caused by this disease. ***Cancer* 1999;86:37–42.**

KEYWORDS: antioxidants, supplementation, β-carotene, α-tocopherol, pancreatic carcinoma, prevention, clinical trial.

The prognosis of patients with carcinoma of the pancreas remains very poor; 97–98% of patients die of the disease despite all efforts to improve the diagnostic and therapeutic armament.[1] Only a few definitive causal factors for carcinoma of the pancreas have been identified.[2–4] The most consistent one is cigarette smoking, which has been estimated to increase the risk two- to fourfold[4–6] but to explain less than one-sixth of the incidence.[7] Possible etiologic factors include various dietary components, diabetes, chronic pancreatitis, occupational exposures, alcohol consumption, and certain other medical conditions and procedures.[3] Although the dietary components suspected to play a role in the development of carcinoma of the pancreas appear to include protective factors as well, they have so far offered no framework for practical preventive measures.

The Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study was a randomized, placebo-controlled, double-blind trial in which the efficacy of α-tocopherol and β-carotene was tested in the primary prevention of cancer.[8] This report describes the effects of the supplementation on the rates of incidence of and mortality from carcinoma of the pancreas.

MATERIALS AND METHODS

The details of the study objectives, design, and methods and the characteristics of the study participants have been published.[8] The study was approved by the institutional review boards of the participating institutions, and all participants signed an informed consent prior to entry. Participants' interests were attended to by an independent Data and Safety Monitoring Committee, which convened biannually during the trial.

Participants

Eligibility for the ATBC Study required smoking at least five cigarettes daily, no prior cancer, no other serious disease, and no use of vitamin E, A, or β-carotene supplements in excess of predefined doses. The 29,133 participants were male smokers who were ages 50–69 years at the time they were randomized to 1 of the 4 intervention groups: dl-α-tocopherol (AT; 50 mg/day), β-carotene (BC; 20 mg/day), both AT and BC (ATBC), or placebo. This design allowed analysis of the results in halves of the total population: those supplemented with β-carotene (BC + ATBC) compared with those who did not receive β-carotene (AT + placebo) and those supplemented with α-tocopherol (AT + ATBC) compared with those who did not receive α-tocopherol (BC + placebo). Double-blind supplementation continued until death or April 30, 1993, and lasted for 5–8 years (median, 6.1 years).

METHODS

Baseline assessment included medical, dietary, smoking, and occupational histories; measurements of height and weight; and serum sampling. Dietary intakes of total energy, fat, protein, carbohydrates, fiber, fruits, vegetables, coffee, tea, vitamin A, vitamin C, vitamin E, β-carotene, and alcohol were calculated from a diet history questionnaire[9] utilizing comprehensive nutrient data.[10] Serum α-tocopherol and β-carotene levels were determined by high performance liquid chromatographic analyses.[11]

After randomization the participants made three visits annually to the local study centers. During the follow-up visits the men were asked about their illnesses and contacts with the medical care system, smoking habits, and self-perceived symptoms and skin yellowing. Specially trained registered nurses took care of all the study contacts with the participants.

Cancer cases were identified through the Finnish Cancer Registry and the Register of Causes of Death. Cases known to have been diagnosed up to April 30, 1993 (n = 89) are included in this report. Verification of diagnosis was based on medical records and pathology specimens collected and compiled during the treatment of the patients. Medical records of all cases were centrally reviewed by at least two study oncologists for verification of the diagnosis of carcinoma of the pancreas.

The relevant histopathologic and cytologic specimens of the cancer cases were collected from the pathology laboratories. Slides for 64 cases (72%) were available for a review by a study pathologist to verify the existence and type of cancer. The histopathologic type was adenocarcinoma in 94% of the cases with a histologic or cytologic specimen. Histologic or cytologic specimens of 9 cases were not available for review, and in these cases the primary diagnosis of the hospital pathologist was used; 89% were adenocarcinomas. In all, the diagnosis was based on histology in 61%, cytology in 21%, and clinical information only in 18% of the cases, with no differences between supplementation groups in diagnostic methods.

Rates of incidence of and mortality from carcinoma of the pancreas were modelled using the Cox proportional hazards model. Proportional hazards assumption was checked using the method of Therneau et al.[12] Interaction of the trial intervention effects were tested in a Cox model. Yellowing of the skin was modelled by treating yellowing as a time-dependent covariate with robust variance estimators used in the Cox regression models.[13] Effects are reported as relative risks (RRs) and corresponding 95% confidence intervals (CIs).

RESULTS

Baseline characteristics of the participants are presented in Table 1. There were no differences between the four intervention groups in the basic personal properties or known risk factors for carcinoma of the pancreas. The dropout rate during the follow-up was

TABLE 1
Baseline Characteristics of the Study Population by Intervention Group (n = 29133): Mean Values (with Standard Deviations) or Proportions (%)

Baseline characteristics	AT (n = 7286)	BC (n = 7282)	ATBC (n = 7278)	Placebo (n = 7287)
Age (yrs)	57.7 (5.1)	57.8 (5.1)	57.8 (5.0)	57.6 (5.1)
Regular smoking (yrs)	35.9 (8.5)	36.0 (8.5)	35.9 (8.5)	35.9 (8.4)
No. of cigarettes/day	20.6 (8.8)	20.4 (8.9)	20.4 (8.9)	20.4 (8.7)
Serum				
α-tocopherol (mg/L)	11.9 (3.7)	12.0 (3.7)	12.0 (3.4)	11.9 (3.5)
β-carotene (μg/L)	214.3 (422.9)	212.6 (185.9)	218.0 (424.9)	211.4 (182.5)
Retinol (μg/L)	586.9 (131.7)	588.6 (134.0)	587.8 (128.0)	589.5 (129.1)
Total cholesterol (mmol/L)	6.2 (1.2)	6.2 (1.2)	6.2 (1.2)	6.2 (1.2)
Intake				
Total energy (kcal)	2817 (784)	2819 (795)	2816 (781)	2808 (788)
Fat (g/day)	123 (41)	123 (41)	123 (41)	123 (41)
Protein (g/day)	103 (29)	103 (30)	103 (29)	103 (30)
Carbohydrates (g/day)	304 (95)	304 (96)	304 (94)	303 (96)
Total fiber (g/day)	26 (10)	26 (10)	26 (10)	26 (10)
Vitamin E (mg/day)	12.0 (5.7)	12.1 (5.8)	12.1 (5.7)	12.0 (5.7)
β-carotene (mg/day)	2.1 (1.6)	2.1 (1.6)	2.1 (1.5)	2.2 (1.5)
Vitamin A (mg/day)	1.8 (1.5)	1.8 (1.5)	1.9 (1.5)	1.8 (1.5)
Alcohol (g/day)	18.1 (21.6)	18.0 (22.0)	17.8 (21.2)	18.0 (21.5)
BMI (kg/m^2)	26.3 (3.8)	26.2 (3.8)	26.3 (3.7)	26.3 (3.9)
Allergic eczema[a] (%)	7.9	7.1	7.3	7.2
Bronchial asthma[a] (%)	3.1	3.4	2.8	3.1
Gallstones[a] (%)	5.4	5.3	5.7	5.7
Pancreatitis[a] (%)	1.7	1.5	1.3	1.4
Peptic or duodenal ulcer[a] (%)	17.6	17.5	17.4	17.5
Diabetes[a] (%)	4.1	4.5	4.6	3.8

AT: α-tocopherol only; BC: β-carotene only; ATBC: α-tocopherol and β-carotene combined; BMI: body mass index.
[a] Self-reported diagnosis made by a physician.

31% (n = 3570, including deaths) and similar in the intervention groups.

Compliance with intervention, measured as capsule disappearance, was equally excellent in the intervention groups; the median was 99%. Of the active participants, 80% took more than 95% of their capsules. Highly group specific serum response in the concentrations of α-tocopherol and β-carotene confirmed the good compliance.[8]

The total number of incident cases of carcinoma of the pancreas was 89. There were 25 cases in the group that received AT alone, 12 cases in the group that received BC alone, 26 cases in the combination group, and 26 cases in the placebo group. Neither supplementation had a statistically significant effect on the rate of incidence of carcinoma of the pancreas. The rate of incidence of carcinoma of the pancreas was 25% (95% CI, −51% to 14%) lower among the men who received β-carotene supplements compared with the men who did not receive them and 34% (95% CI, −12% to 105%) higher among the men who received α-tocopherol compared with those who did not receive them. It is noteworthy that analysis of the original four intervention groups reveal a somewhat different picture. The relative risk for carcinoma of the pancreas was −4% (95% CI, −44% to 67%) for AT, −54% (95% CI, −77% to −8%) for BC, 0% (95% CI, −48% to 73%) for ATBC compared with placebo. The formal test for interaction between AT and BC was not statistically significant.

There appeared to be no obvious evidence of possible diagnostic shifts and misclassification of carcinoma of the pancreas as another primary cancer in the BC group. There were no excess cancers of the liver, gallbladder and bile ducts, or unknown primary organ in the BC group. The number of lung adenocarcinomas was 34 in the BC group, 29 in the AT alone and placebo groups, and 22 in the ATBC group. On the other hand, there were no intervention group differences in survival times for lung adenocarcinoma, being 2−3 times longer than those observed for carcinoma of the pancreas cases.

The primary reasons for seeking medical attention and initiating investigations that led to a diagnosis of carcinoma of the pancreas were quite similar in all intervention groups. Symptoms that were systemic or due to local tumor effects or metastases were present in about 90% of cases. The cancer was found by

TABLE 2
Number of Cases, Rate of Incidence (per 1000 person-years), Relative Risk, Median Survival Times after Diagnosis, and Mortality from Pancreatic Carcinoma during Follow-Up by Supplementation

	Supplementation			
	AT	No AT	BC	No BC
No. of cases	51	38	38	51
Rate of incidence	0.60	0.45	0.45	0.60
Relative risk	1.34	1.00	0.75	1.00
95% CI	0.88–2.05	—	0.49–1.14	—
No. of deaths	49	34	35	48
Specific mortality[a]	1.11	1.00	0.81	1.00
95% CI	0.72–1.72	—	0.53–1.26	—
Survival time (days)	144	149	162	134

AT: α-tocopherol group and α-tocopherol plus β-carotene group; No AT: β-carotene group and placebo group; BC: β-carotene group and α-tocopherol plus β-carotene group; No BC: α-tocopherol group and placebo group; CI: confidence interval.
[a] Expressed as relative risk, adjusted for stage and location of the tumor.

chance in autopsy or surgery in 4% of cases in all other intervention groups but the BC group, in which there were no autopsy cases.

At the time of diagnosis, carcinoma of the pancreas was Stage I or II (local) in 25% of the patients, Stage III (regional) in 9%, Stage IV (distant) in 53%, and in 13% stage could not be defined due to lack of information. Case fatality during follow-up was associated with stage. The relative risk of dying from carcinoma of the pancreas was 3.1 (95% CI, 1.6–5.9) with Stage IV tumors compared with Stage I–II tumors when supplementation and location of the tumor (head or other) were taken into account. The intervention groups were not completely balanced with respect to stage distribution; there were no patients with tumors of undefined stage in the BC group. On the other hand, the risk of dying from a tumor of undefined stage during the trial was 0.8 (95% CI, 0.4–1.8), and grouping these cases together with those of Stage I–II was justified, balancing the stage distribution of the intervention groups. The tumor was located in the head of pancreas in 14% of cases in the BC group, in 33% in the AT group, in 26% in the ATBC group, and in 28% in the placebo group.

During follow-up, 83 men died from carcinoma of the pancreas. Neither supplementation had a statistically significant effect on the rate of mortality from this disease. Mortality from carcinoma of the pancreas during follow-up, adjusted for stage and location of the tumor (head or other), was 19% lower among those who received BC supplementation (n = 35) compared with those not who did not receive BC (n = 48) (95% CI, −47% to 26%). The α-tocopherol supplementation (n = 49) increased the rate of mortality by 10% (95% CI, –28% to 72%) compared with those who did not receive α-tocopherol (Table 2). The median survival time after diagnosis during follow-up was slightly longer among those who received BC supplementation compared with the other groups, but this was mainly due to few individuals' having a long survival time after radical surgery. Of the six survivors, three were from the BC group, two were from the AT group, and one was from the placebo group.

High dietary intake of vitamin E and β-carotene and serum levels of α-tocopherol and β-carotene at baseline were not associated with a statistically significantly lower risk of carcinoma of the pancreas during follow-up when supplementation and baseline age, smoking years, number of daily cigarettes, and intake of vitamin C were taken into account. The risk in the highest tertiles of intake compared with the lowest tertile were 0.9 (95% CI, 0.5–1.6) and 1.3 (95% CI, 0.7–2.5) for α-tocopherol and β-carotene, respectively. Similarly, the relative risks for subsequent carcinoma of the pancreas were 0.9 (95% CI, 0.5–1.5) and 0.6 (95% CI, 0.4–1.1) in the highest tertiles of serum α-tocopherol and β-carotene, respectively.

The baseline characteristics, including smoking and alcohol intake, did not modify the effects of the supplementations (data not shown). Certain baseline characteristics were also evaluated as possible independent risk factors for carcinoma of the pancreas. History of allergy, gallstones, peptic or duodenal ulcer, or diabetes did not increase the risk of this cancer.

Because yellowing of the skin is a possible sign of carcinoma of the pancreas (jaundice) and is also a possible consequence of β-carotene ingestion (carotenodermia), special attention was paid to this phenomenon. The number of cases reporting skin yellowing at least once before diagnosis during the follow-up was two among those taking β-carotene, one taking α-tocopherol, seven taking both supplementations, and two taking placebo. Skin yellowing was not associated with an increased risk of carcinoma of the pancreas regardless of the supplementation group. Among those 12 cases in which skin yellowing was reported before diagnosis, there were no obvious group specific differences in the lag times from the first appearance of the skin yellowing to the diagnosis of carcinoma of the pancreas. The lag times varied from 16 to over 2000 days.

DISCUSSION

The results of this study suggest that supplementation with β-carotene or α–tocopherol does not have major effects on the rate of incidence of carcinoma of the pancreas among older men who smoke. The results based on the original four intervention groups offer a tempting conclusion regarding the beneficial effects of β-carotene. Although the prospect of prevention of a highly lethal cancer is exciting, there are several reasons for prudence. Pancreatic carcinoma was not one of the a priori endpoints for cancer prevention in the ATBC Study. The number of carcinoma of the pancreas cases was relatively small, and thus the possibility of a chance finding cannot be neglected. Furthermore, α–tocopherol appeared to wipe out the β-carotene effect as a statistically significant phenomenon. On the other hand, supplementation both lowered the rates of incidence and specific mortality and increased the survival time.

There are no known mechanisms to explain the preventive effect of BC on carcinoma of the pancreas, histologically primarily adenocarcinoma. Most of the available epidemiologic evidence of the benefits of BC is related to squamous cell malignancies.[14–16] There are several possible mechanisms for the general antitumorigenic action of BC, but none of them relate solely and directly to the pancreas as the site of action.[17–22] There have been no prior reports of the effects of BC or other micronutrient supplementation on carcinoma of the pancreas. The results concerning dietary intake of BC and risk of carcinoma of the pancreas are not consistent.[23] In some studies, high intake of BC is associated with lower risk;[24,25] some have found similar associations with the intake of fruits and vegetables,[26,27] whereas others have not.[6,28] Also, in two small nested case–control studies[29,30] and one small cohort study,[31] low serum concentration of BC or total carotenoids at baseline were not associated with subsequent risk of carcinoma of the pancreas. Serum concentrations of α-tocopherol were associated with a lower risk of carcinoma of the pancreas in one study.[32] There are no reports specifically of vitamin E intake in relation to this disease.

The finding that the combination of BC and AT did not have any effect is intriguing and biologically complicated. It suggests that, given that the effect of BC is true, there exists an interaction between AT and BC, possibly on the molecular level, so that AT blocks the effects of BC. Excessive amounts of α-tocopheroxyl radical could bind BC that is needed to regenerate the radical form back to functional AT,[33] thus making less BC available. It has also been suggested that simultaneous supplementation with β-carotene and α-tocopherol could compromise the achievable tissue concentrations of the individual substances; but several reports, including one from the ATBC Study, have shown that this does not happen.[34–37]

Bias is a very unlikely explanation for the results in a large, randomized, double-blind, and controlled trial with premium capsule compliance, similar dropout rates in intervention groups, and comprehensive endpoint verification. One potential source of bias related to the supplementation, however, is skin yellowing due to β-carotene. The number of men reporting persistent skin yellowing was small and the phenomenon was not related to the diagnostic procedures. Pancreatic carcinoma progresses rapidly and is such a lethal disease that a possible change in the time frame of the diagnostic process is unlikely to influence the observed rate of incidence during the follow-up and cause bias.

A diagnostic shift could be another explanation for the low rate of incidence of carcinoma of the pancreas in the BC group. Very early on, before becoming clinically apparent, carcinoma of the pancreas typically seeds metastases into liver, lungs, and bones.[38] The lymph nodes seen in the chest X-ray of a severely ill patient and found to be adenocarcinoma could be taken as a diagnostic finding of lung malignancy. The need to verify the diagnosis might be less pressing with such a rapidly progressing and fatal process as carcinoma of the pancreas. However, there is no apparent reason why this phenomenon, if present, should be limited to those men taking BC only. All the available information on the clinical histories of cases indicated no group differences in the diagnostic methods used.

In conclusion, the rate of incidence of carcinoma of the pancreas among men supplemented daily with 20 mg of BC or 50 mg of AT for 5–8 years was not statistically different from the rate of incidence among men who did not receive the supplementation.

REFERENCES

1. Wanebo HJ, Vezeridis MP. Pancreatic carcinoma in perspective: a continuing challenge. *Cancer* 1996;78(3 Suppl):580–91.
2. Boyle P, Hsieh CC, Maisonneuve P, La Vecchia C, Macfarlane GJ, Walker AM, et al. Epidemiology of pancreas cancer (1988). *Int J Pancreatol* 1989;5:327–46.
3. Haddock G, Carter DC. Aetiology of pancreatic cancer. *Br J Surg* 1990;77:1159–66.
4. Friedman GD, van den Eeden SK. Risk factors for pancreatic cancer: an exploratory study. *Int J Epidemiol* 1993;22:30–7.
5. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. A case–control study of pancreatic cancer and cigarettes, alcohol, coffee and diet. *Am J Public Health* 1989; 79:1016–9.
6. Zheng W, McLaughlin JK, Gridley G, Bjelke E, Schuman LM, Silverman DT, et al. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). *Cancer Causes Control* 1993;4:477–82.
7. Fernandez E, La Vecchia C, Decarli A. Attributable risks for pancreatic cancer in northern Italy. *Cancer Epidemiol Biomarkers Prev* 1996;5:23–7.

8. The ATBC Cancer Prevention Study Group. The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. *Ann Epidemiol* 1994;4:1–10.
9. Pietinen P, Hartman A, Haapa E, Räsänen L, Haapakoski J, Palmgren J, et al. Reproducibility and validity of dietary assessment instruments. *Am J Epidemiol* 1988;128:655–66.
10. Ovaskainen M-L, Lauronen J, Haapakoski J. Epidemiological food and nutrient database at the National Public Health Institute. *Scand J Nutr* 1994;38:10.
11. Milne D, Botnen J. Retinol, alpha/tocopherol, lycopene, and alpha- and beta-carotene simultaneously determined in plasma by isocratic liquid chromatography. *Clin Chem* 1986; 32:874–6.
12. Therneau TM, Grambsch PM, Fleming TR. Martingale-based residuals for survival models. *Biometrika* 1990;77: 147–60.
13. Lee EW, Wei LJ, Amato D. Cox-type regression analysis for large number of small groups correlated failure time observations. In: Klein JP, Goel PK. Survival analysis: state of the art. The Netherlands: Kluwer Academic Publishers, 1992: 237–47.
14. Rautalahti M, Huttunen J. Antioxidants and carcinogenesis. *Ann Med* 1994;26:435–41.
15. Gerster H. Beta-carotene, vitamin E and vitamin C in different stages of experimental carcinogenesis. *Eur J Clin Nutr* 1995;49:155–68.
16. Patterson RE, White E, Kristal AR, Neuhouser ML, Potter JD. Vitamin supplements and cancer risk: the epidemiologic evidence. *Cancer Causes Control* 1997;8:786–802.
17. Burton G, Ingold K. Beta-carotene: an unusual type of lipid antioxidant. *Science* 1984;224:569–73.
18. Pung A, Rundhaug JE, Yoshizawa CN, Bertram JS. Beta-carotene and canthaxanthin inhibit chemically and physically induced neoplastic transformation in 10T1/2 cells. *Carcinogenesis* 1988;9:1533–9.
19. Zhang LX, Acevedo P, Guo H, Bertram JS. Upregulation of gap junctional communication and connexin43 gene expression by carotenoids in human dermal fibroblasts but not in human keratinocytes. *Mol Carcinog* 1995;12:50–8.
20. Tomita Y, Himeno K, Nomoto K, Endo H, Hirohata T. Augmentation of tumor immunity against syngeneic tumors in mice by beta-carotene. *J Natl Cancer Inst* 1987;78:679–81.
21. Gradelet S, Leclerc J, Siess MH, Astorg PO. Beta-Apo-8′-carotenal, but not beta-carotene, is a strong inducer of liver cytochromes P4501A1 and 1A2 in rat. *Xenobiotica* 1996;26: 909–19.
22. Buttke TM, Sandstrom PA. Oxidative stress as a mediator of apoptosis. *Immunol Today* 1994;15:7–10.
23. Howe GR, Burch JD. Nutrition and pancreatic cancer. *Cancer Causes Control* 1996;7:69–82.
24. Howe GR, Ghadirian P, Bueno de Mesquita HB, Zatonski WA, Baghurst PA, Miller AB, et al. A collaborative case–control study of nutrient intake and pancreatic cancer within the search programme. *Int J Cancer* 1992;51:365–72.
25. Ji BT, Chow WH, Gridley G, McLaughlin JK, Dai Q, Wacholder S, et al. Dietary factors and the risk of pancreatic cancer: a case–control study in Shanghai China. *Cancer Epidemiol Biomarkers Prev* 1995;4:885–93.
26. Gold EB, Gordis L, Diener MD, Seltser R, Boitnott JK, Bynum TE, et al. Diet and other risk factors for cancer of the pancreas. *Cancer* 1985;55:460–7.
27. Falk RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF Jr. Life-style risk factors for pancreatic cancer in Louisiana: a case–control study. *Am J Epidemiol* 1988;128:324–36.
28. Mills PK, Beeson WL, Abbey DE, Fraser GE, Phillips RL. Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. *Cancer* 1988;61: 2578–85.
29. Burney PG, Comstock GW, Morris JS. Serologic precursors of cancer: serum micronutrients and the subsequent risk of pancreatic cancer. *Am J Clin Nutr* 1989;49:895–900.
30. Knekt P, Aromaa A, Maatela J, Aaran RK, Nikkari T, Hakama M, et al. Serum vitamin A and subsequent risk of cancer: cancer incidence follow-up of the Finnish Mobile Clinic Health Examination Survey. *Am J Epidemiol* 1990;132:857–70.
31. Eichholzer M, Stahelin HB, Gey KF, Ludin E, Bernasconi F. Prediction of male cancer mortality by plasma levels of interacting vitamins: 17-year follow-up of the prospective Basel study. *Int J Cancer* 1996;66:145–50.
32. Knekt P, Aromaa A, Maatela J, Alfthan G, Aaran RK, Teppo L, et al. Serum vitamin E, serum selenium and the risk of gastrointestinal cancer. *Int J Cancer* 1988;42:846–50.
33. Bohm F, Edge R, Land EJ, McGarvey DJ, Truscott TG. Carotenoids enhance vitamin E antioxidant efficiency. *J Am Chem Soc* 1997;119:621–2.
34. Willett WC, Stampfer MJ, Underwood BA, Taylor JO, Hennekens CH. Vitamins A, E, and carotene: effects of supplementation on their plasma levels. *Am J Clin Nutr* 1983;38: 559–66.
35. Nierenberg DW, Stukel TA, Baron JA, Dain BJ, Greenberg ER. Determinants of plasma levels of beta-carotene and retinol. Skin Cancer Prevention Study Group. *Am J Epidemiol* 1989; 130:511–21.
36. Goodman GE, Metch BJ, Omenn GS. The effect of long-term beta-carotene and vitamin A administration on serum concentrations of alpha-tocopherol. *Cancer Epidemiol Biomarkers Prev* 1994;3:429–32.
37. Albanes D, Virtamo J, Taylor PR, Rautalahti M, Pietinen P, Heinonen OP. Effects of supplemental beta-carotene, cigarette smoking, and alcohol consumption on serum carotenoids in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Clin Nutr* 1997;66:366-72.
38. Howard TJ. Pancreatic adenocarcinoma. *Curr Probl Cancer* 1996;20:281–328.